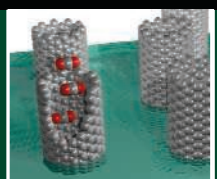

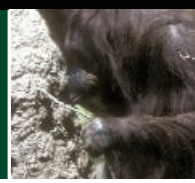

LETTERS

edited by Etta Kavanagh

Translation Research and Drug Development

JOCELYN KAISER'S RECENT ARTICLE ON "TRANSLATIONAL research" ("A cure for medicine's ailments?," News Focus, 31 Mar., p. 1852) sounded an encouraging note to basic and clinical researchers alike who yearn to test their pet ideas for new cures. According to Kaiser, translational research is loosely defined as "moving a basic discovery into early clinical trials." However, NIH's apparent desire to foster translational research by funding university-based drug development centers sends shivers down this taxpayer's back. Pharma spends upwards of $800 million and takes 10 to 12 years to get a drug from bench to bedside (*1*). Annual R&D investment by pharma has risen from $1 billion to $40 billion since 1975, while annual new drug approvals have remained flat at between 20 and 30. Thus, drug development today is less efficient than 30 years ago, which partly explains the continual rise in drug costs. Although NIH's interest in drug development is laudable, does anybody truly believe that academic translational research centers will be as efficient, let alone competitive, at developing drugs as pharma?

Kaiser pointed to an anecdotal case where a single-minded researcher persevered for years to get a novel anticancer agent tested in a small clinical trial. The implication was that the researcher could have made more rapid progress if her university had invested in more translational research activities. Even if this were true, who will fund the rest of the costly activities required to bring this drug to market? Granted, these activities may fall outside of the accepted view of translational research. But without a funding partner, investing in translational research is akin to building a bridge to nowhere.

The road from the discovery of a drug to the first human clinical trial leads through a painstaking and circuitous route that is tedious and expensive, fails more than 90% of the time, does not lead to front-line publications, and does not constitute the type of research that many deem worthy of a Ph.D. But it will make or break your favorite drug candidate. I believe that a better use of taxpayers' dollars would be to support innovative research proposals related to improving the efficiency of the drug R&D process. In this way, we will lower the time and cost, as well as the failure rate, of bringing new drugs to market, and the public will benefit. And I bet pharma will invest private dollars into these activities. This is the sort of translational research that makes more sense to me—building bridges between academia and pharma—than trying to duplicate pharma activities in academic settings.

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Extinct or Possibly Extinct?

LISTS OF EXTINCT SPECIES OFTEN ACT AS "WAKE-UP calls" and are based on the length of time since the last sighting, resulting in numerous species having been prematurely classified as being extinct only to be rediscovered (*1*). This not only provides ammunition for environmental sceptics (D. S. Wilcove, "Rediscovery of the ivory-billed woodpecker," Perspectives, 3 June 2005, p. 1422) but also undermines potential conservation action and, more worryingly, public support (*2*). It is almost impossible to determine with any certainty whether a species is extinct. Therefore, any statement of extinction is probabilistic by nature (*3*). The rediscovery of the ivory-billed woodpecker [J. W. Fitzpatrick *et al.*, "Ivory-billed woodpecker (*Campephilus principalis*) persists in continental North America," Reports, 3 June 2005, p. 1460] has recently been called into question [(*4*); D. A. Sibley *et al.*, Comment on "Ivory-billed woodpecker (*Campephilus principalis*) persists in continental North America," Technical Comment, 17 Mar., www.sciencemag.org/cgi/content/full/311/5767/1555a]. Even so, it raises the question, which seems to have been missed by scientists, as to whether this species should have been declared extinct in the first place.

The case for classifying the ivory-billed woodpecker as extinct was based on the very long time that had elapsed since the most recent confirmed sighting. Under the IUCN Red List criteria, a species is classified as "extinct" only after exhaustive surveys fail to produce any observations over an appropriate time period and geographical range (*5*). For most species, this is impractical (*2*).

A statistical test for extinction based on the most recent sightings of a species was described by Solow (*6*). If we use the five most recent pre-2004 sightings of the ivory-billed woodpecker (1938, 1939, 1941, 1944, and 1952) (*7*), then the significance level (or *P* value) in testing in 2004 for extinction is 0.186. The hypothesis that the ivory-billed woodpecker is extant should not have been rejected. Even if we take the last sighting to be 1944, as others suggest (*4*), then the significance level is 0.056. This raises the question of whether the IUCN Red List requires a "possibly extinct" category as any statement of extinction is probabilistic by nature.

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Incorporating Evolution into Medical Education

IN THEIR EDITORIAL "MEDICINE NEEDS EVOLUTION" (24 Feb., p. 1071), R. M. Nesse *et al.* highlight human maladies whose origin and expression might be illuminated by evolutionary perspectives. The examples are many, and they point out the need for a central evolutionary insight that can help to inform all of medical thinking and serve as the basis for the integration of evolution into medical education and clinical practice.

Medicine might benefit most from embracing evolution theory's recognition of individual variation within populations of organisms, a property that Ernst Mayr has called "the cornerstone of Darwin's theory of natural selection" (*1*). This "population thinking," as Mayr calls it, helped to undo typological thinking in biology, and it can help to dismantle typological notions of disease by highlighting individual differences in disease susceptibility and expression, as well as variations in response to treatment.

The inextricable relationship between evolution and genetics is evident in current genomic-based efforts such as the HapMap project, which catalogs DNA variants associated with disease, and in the recently announced Genes and Environment Initiative at NIH, which will investigate the interaction of genetic and environmental variations in common diseases. A major challenge for medical education is to incorporate genetics and evolution into education systems where neither receives the attention necessary to make it a routine part of medical thinking or clinical practice.

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Reference

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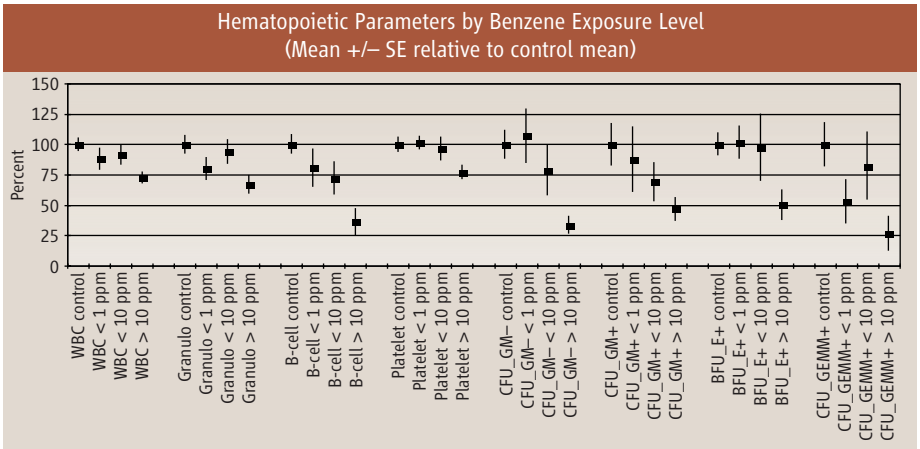
Benzene Exposure and Hematotoxicity

IN THEIR REPORT "HEMATOTOXICITY IN WORKERS exposed to low levels of benzene" (3 Dec. 2004, p. 1774), Q. Lan *et al.* present data on blood cell counts and hematopoietic progenitor cell colony formation from sera of benzene-exposed workers (and controls) in China, from which they conclude that their data demonstrate hematotoxicity with benzene air levels at less than 1 ppm. Although we concur that their data demonstrate hematotoxicity with benzene levels at greater than 10 ppm, we do not observe in their data consistent evidence of hematotoxicity at lower levels.



Hematopoetic parameters by benzene exposure level. Mean (±SE) relative to control mean. Adapted from Lan *et al.*

Their blood cell counts (their table 1) showed a monotonically increasing effect only for platelets and B cells, but not for the measured cell lines that might be expected to lead to myeloid leukemic lines. White blood cell and granulocyte counts that showed a reduction in cell number at less than 1 ppm did not show a further reduction among workers with exposures up to 10 ppm.

The authors' progenitor cell colony formation data (their fig. 1) did not separate out the data below 10 ppm and thus do not demonstrate whether an effect occurred at <1 ppm. They have kindly supplied us those data (our figure). In these data, we observe a suggestive monotonically increasing trend only for granulocyte-macrophage colony-formation (CFU_GM–), which first appears at greater than 1 ppm in the absence of erythropoietin and at less then 1 ppm in the presence of erythropoietin. Neither reduction is statistically significant until the group with benzene exposure at greater than 10 ppm is considered.

We consider the authors' conclusion premature, based only on the difference of reduction in in vitro granulocyte-macrophage colony formation by the addition of erythropoietin to the culture medium. The only implication of the difference of adding erythropoietin is that by driving the formation of the erythroid lineage, they reduce the myeloid colony numbers ("lineage competition").

A demonstration of damage to stem cell function or number would be a more relevant indication of hematotoxicity than is damage to committed progenitor stem cells as proposed by Lan *et al.* We would propose the alternative conclusion that their data show that hematotoxicity as measured by reduction of in vitro colony formation may well be ascribed to levels of benzene greater than 10 ppm but do not justify the implied damage from levels lower than that.

Finally, although the authors' findings of reduction in peripheral granulocytes may carry statistical significance, the numbers they found in their exposed individuals are all fully within the normal range and do not carry clinical significance.

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Response

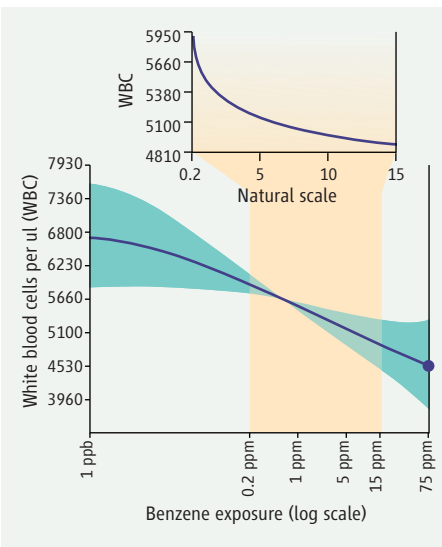
WE REPORTED THAT WHITE BLOOD CELL (WBC) counts were decreased in workers exposed to less than 1 ppm benzene compared with controls and that a highly significant dose-response relationship was present (original Table 1, text). Lamm and Grünwald argue that a monotonic dose-response relationship must be present across higher levels of exposure before one can accept differences between controls and the lowest exposure group. Although we do not necessarily agree with their premise, we confirmed the monotonicity of the association by spline regression analyses of WBC count and benzene exposure and found no apparent threshold within the occu-

pational exposure range of our study (0.2 to 75 ppm benzene; see our figure).

Another goal of our study was to determine whether benzene was associated with a decrease in progenitor cells across a wide range of exposure, and whether progenitor cells were more sensitive to the effects of benzene than mature cells. We found highly statistically significant, inverse dose-dependent trends for all progenitor cells and observed that a number of progenitor cells, including CFU-GEMM colonies, were significantly more sensitive to the effects of benzene than peripheral WBC or granulocyte counts among highly exposed workers (original fig. 1). Lamm and Grünwald show progenitor colony data for each exposure category and break out effects for the <1 ppm group, even though there are only 8 subjects in this category (their figure), and report that colony counts in this group were not significantly different from controls. A substantially larger study would be needed to address this question, which was not a goal of our paper. In addition, they present data on WBC and other cell counts for the subgroup of 53 subjects with progenitor colony data (their figure); conclusions based on benzene exposure and mature blood cell counts should be based on the entire data set (original Table 1; our figure) rather than on this subgroup.

Lamm and Grünwald suggest that it would have been worthwhile to culture stem cells. Although data of this type would be of interest, it was not feasible to collect in the occupational setting, and CFU-GEMM, CFU-GM, and BFU-E are commonly used surrogates for stem cell measurements.

Finally, we note that changes of the magnitude we report for mature blood cells are generally considered unlikely to have immediate clinical consequences. However, as we show even more pronounced effects in progenitor cells, there is a concern that the overall pattern of hematologic changes we observe could reflect events in bone marrow that may be associated with health effects in the future, particularly among genetically susceptible subpopulations (*1*–*3*).



Plot shows the dose-response curve (line) and 95% pointwise confidence limits (shaded areas) for differences between white blood cell (WBC) count at a given air benzene exposure versus WBC level at a reference dose of 0.6 ppm (median benzene exposure level of the total study population). Graph shows the fitted nonparametric response curve using generalized additive models (*4*) on a natural scale versus benzene exposure on a log scale (truncated at 1 ppb); inset graph shows the fitted nonparametric response curve on a natural scale versus benzene exposure between 0.2 and 15 ppm on a natural scale. The nonparametric curve was fitted using a regression spline with 1 segment, which was the optimal number of polynomial segments (1 to 5 tested) based on the Akaike Information Criterion (*5*). The model was adjusted for the same variables used in previous analyses (original table 1). Complete data from 139 controls and 247 exposed subjects were available. Data were used from only the first study year for subjects with repeat measures in the second study year. Using data from only the second year for these subjects resulted in essentially the same prediction models. Air benzene exposure among the controls was estimated based on the linear relation of log urinary benzene levels on log air benzene (*6*). The slope of the spline function was significantly less than zero for every point between 0.2 and 15 ppm, indicating that the geometric mean WBC count decreased significantly with increasing exposure over this specific exposure range ($P < 0.05$, accounting for multiple comparisons).

QING LAN,[1] ROEL VERMEULEN,[1] LUOPING ZHANG,[2] GUILAN LI,[3] PHILIP S. ROSENBERG[1], BLANCHE P. ALTER,[1] MIN SHEN,[1] STEPHEN M. RAPPAPORT,[4] RONA S. WEINBERG,[5] STEPHEN CHANOCK,[1,6] SURAMYA WAIDYANATHA,[4] CHARLES RABKIN,[1] RICHARD B. HAYES,[1] MARTHA LINET,[1] SUNGKYOON KIM,[4] SONGNIAN YIN,[3] NATHANIEL ROTHMAN,[1] MARTYN T. SMITH[2]

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CORRECTIONS AND CLARIFICATIONS

NetWatch: "All physics, all the time" (28 Apr., p. 505). The item incorrectly stated that Bowling Green State University is in Kentucky. It is in Ohio.

ScienceScope: "NYU gift kicks up more dust" by M. Balter (28 Apr., p. 513). The URL for the "Statement of Concern" mentioned in the item was incorrect. It should be www.bib-arch.org/bswbOOunprovenanced.html.

News of the Week: "Opening the door to a chilly new climate regime" by R. A. Kerr (21 Apr., p. 350). The current abbreviated "ACC" was incorrectly identified. It is the Antarctic Circumpolar Current.

Special Section News: "A one-size-fits-all flu vaccine?" by J. Kaiser (21 Apr., p. 380). The table is missing a symbol indicating that "DNA vaccine with NP, sometimes M2 genes" stimulates cytotoxic T lymphocytes.

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "The Brain of LB1, *Homo floresiensis*"

R. D. Martin, A. M. MacLarnon, J. L. Phillips, L. Dussubieux, P. R. Williams, W. B. Dobyns

Endocast analysis of the brain *Homo floresiensis* by Falk *et al*. (Reports, 8 April 2005, p. 242) implies that the hominid is an insular dwarf derived from *H. erectus*, but its tiny cranial capacity cannot result from normal dwarfing. Consideration of more appropriate microcephalic syndromes and specimens supports the hypothesis of modern human microcephaly.

Full text at www.sciencemag.org/cgi/content/full/312/5776/999b

RESPONSE TO COMMENT ON "The Brain of LB1, *Homo floresiensis*"

Dean Falk, Charles Hildebolt, Kirk Smith, M. J. Morwood, Thomas Sutikna, Jatmiko, E. Wayhu Saptomo, Barry Brunsden, Fred Prior

Martin *et al*. claim that they have two endocasts from microcephalics that appear similar to that of LB1, *Homo floresiensis*. However, the line drawings they present as evidence lack details about the transverse sinuses, cerebellum, and cerebral poles. Comparative measurements, actual photographs, and sketches that identify key features are needed to draw meaningful conclusions about Martin *et al.*'s assertions.

Full text at www.sciencemag.org/cgi/content/full/312/5776/999c